

⑬ 日本国特許庁 (JP)
⑭ 公開特許公報 (A)

⑮ 特許出願公開
昭55—124763

⑯ Int. Cl.³
C 07 D 213/64
213/70

識別記号
庁内整理番号
7138—4C
7138—4C

⑰ 公開 昭和55年(1980)9月26日

発明の数 1
審査請求 未請求

(全 3 頁)

⑱ 5-トリフルオロメチル-2-ピリドン誘導体

⑲ 特 願 昭54—32068
⑳ 出 願 昭54(1979)3月19日
㉑ 発 明 者 西山隆三
高槻市真上町5丁目41番22号
㉒ 発 明 者 藤川政一
守山市浮気町321番地の31
㉓ 発 明 者 横道勲
草津市野村町221番地

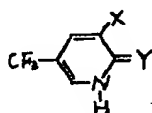
㉔ 発 明 者 芳賀隆弘
草津市野村町221番地
㉕ 発 明 者 長谷邦昭
守山市浮気町321番地の31
㉖ 発 明 者 林弘仁
守山市浮気町321番地の31
㉗ 出 願 人 石原産業株式会社
大阪市西区江戸堀1丁目3番11号

明 細 書

1. 発明の名称 5-トリフルオロメチル-2-
ピリドン誘導体

2. 特許請求の範囲

㉘ 一般式

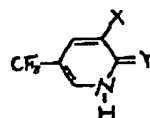


(式中Xは水素原子又はハロゲン原子であり、Yは酸素原子又はイオウ原子である。但し、Xが水素原子の場合、Yはイオウ原子である。)で表わされる5-トリフルオロメチル-2-ピリドン誘導体。

3. 発明の詳細な説明

本発明は医薬、農薬、染料などの中間原料として有用で、新規な5-トリフルオロメチル-2-ピリドン誘導体に関する。

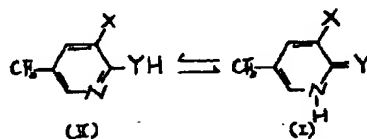
詳しくは本発明は一般式



(I)

(式中Xは水素原子又はハロゲン原子であり、Yは酸素原子又はイオウ原子である。但し、Xが水素原子の場合、Yはイオウ原子である。)で表わされる5-トリフルオロメチル-2-ピリドン誘導体である。

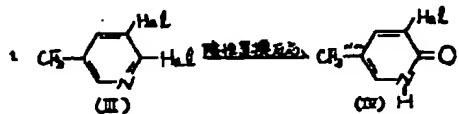
前記一般式(I)の5-トリフルオロメチル-2-ピリドン誘導体は、次に示すような互変異性として存在することができる。



(式中X及びYは前記の通りである)

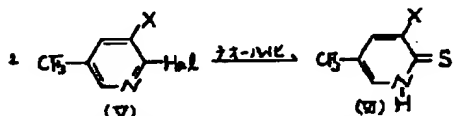
前記一般式(I)において、Xで表わされるハロゲン原子としては弗素、塩素、臭素、沃素が挙げられる。

本発明の5-トリフルオロメチル-2-ビリ
ドン誘導体は通常、例えば下記方法によって製
造される。



(上記反応式中 Hs はハロゲン原子である)

一般に上記反応はジメチルスルホキシド、ジ
メチルホルムアミドなどの非プロトン性極性溶
媒中、水酸化ナトリウム、水酸化カリウムなど
のアルカリ水溶液を用いて50~150℃、0.1
~10時間で行なわれる。



(上記反応式中 X 及び Hs は前述の通りで
ある)

一般に上記反応はメタノール、エタノールな
どのアルコール類、ジメチルスルホキシド、ジ
メチルホルムアミドなどの非プロトン性極性溶

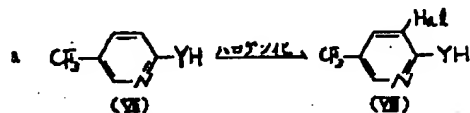
- 3 -

媒とを反応させることによりN-ベンゾイ
ル-N'-[4-(5-トリフルオロメチルビリ
ジン-2-イルオキシ)フェニル]ウレア系化
合物に誘導できる。詳しくは本発明化合物の3
-クロロ-5-トリフルオロメチル-2-ビリ
ドンと3,4,5-トリクロロニトロベンゼンとを
縮合、還元して3,5-ジクロロ-4-(3-ク
ロロ-5-トリフルオロメチルビリジン-2-
イルオキシ)アニリンを得、更にこのものと2
,6-ジフルオロベンゾイルイソシアネートとを
反応させると、N-(2,6-ジフルオロベンゾ
イル)-N'-[3,5-ジクロロ-4-(3-ク
ロロ-5-トリフルオロメチルビリジン-2-
イルオキシ)フェニル]ウレアを得ることがで
きる。このものは殺虫剤の有効成分として優れた
活性を示し、種々の有害虫、特に有害昆虫の
防除に有効であって、例えばこの化合物100
ppm水分散液にキャベツの葉片を浸漬し、それ
を風乾してそこへ2~3台のコナガの幼虫を放
ち、8日目に生死を判定した結果、100%の

- 5 -

H44055-124763(2)

殺などの溶液中、チオ尿素、硫化ソーダ、チオ
硫酸ソーダ、N,N-ジメチルジチオカルバミ
ン酸ソーダなどのチオール化剤を用いて50~
室温温度0.5~10時間で行なわれる。



(上記反応式中 Y 及び Hs は前述の通りである)

一般に上記反応は四塩化炭素、クロロホルム、
酢酸、二硫化炭素、水、非プロトン性極性溶媒
などの溶液中、塩素ガス、臭素、チオニクロ
ライド、スルフリルクロライドなどのハロゲン
化剤を用いて0~100℃、0.5~10時間で行な
われる。

本発明化合物は、例えばハロゲン化ニトロベ
ンゼン類と縮合させて4-(5-トリフルオロ
メチルビリジン-2-イルオキシ)ニトロベン
ゼン類を生成させ、これを還元して得られる4
-(5-トリフルオロメチルビリジン-2-イ
ルオキシ)アニリン類とベンゾイルイソシア

- 4 -

死虫率が得られた。

次に本発明化合物の具体的合成例を記載する。

合成例1 3-クロロ-5-トリフルオロメチ
ル-2-ビリドン

(A)

5-トリフルオロメチル-2-ビリドン0
2gをクロロホルム20mlに溶解させ、50
℃に加温して塩素ガスを1時間攪拌下に通じ
た。反応終了後、クロロホルムを留去し、ト
ルエン-n-ヘキサンの混合溶媒で再結晶し
て融点144~147℃の目的物0.15gを
得た。

(B)

水酸化ナトリウム2.4gを水12.5mlに溶
解させた水溶液に2,3-ジクロロ-5-トリ
フルオロメチルビリジン4gを加え、更にジ
メチルスルホキシド12.5mlを加えて加熱し、
110℃で1時間攪拌下に反応させた。反応
終了後生成物を放冷し、最少量で酸性にして
沈殿物を、このものを濾過して目的 2.5

- 6 -

ヲを た。

合成例 2 5-トリフルオロメチル-2-チオ
ピリドン

2-クロロ-5-トリフルオロメチルピリ
ジン 4g とチオ尿素 1.67g とをエタノール
30ml に溶解させ、加熱して還流状態で3時
間煮沸下に反応させた。その後、水酸化カリ
ウム水溶液 1.23g を徐々に加えて還流状態
で1時間反応させた。反応終了後、生成物を
放冷し、希アルカリ水溶液中に投入して塩化
メチレンで洗浄し、酢酸で酸性にした。次い
で、塩化メチレンで抽出し、抽出層を水洗後
無水硫酸ナトリウムで乾燥させ、塩化メチレ
ンを留去して融点 147~150℃ の目的物
2.1g を得た。

合成例 3 3-ブロモ-5-トリフルオロメチ
ル-2-ピリドン

5-トリフルオロメチル-2-ピリドン 0.
4g を酢酸 10ml に溶解させ、そこへ臭素 0.
4g を加えて攪拌下で4時間反応させた。反

- 7 -

特開昭55-124783(3)

応終了後、酢酸を留去し、塩化メチレン-ロ
-ヘキサンの混合溶液で再結晶して融点 162
~165℃ の目的物 0.45g を得た。

合成例 4 3-クロロ-5-トリフルオロメチ
ル-2-チオピリドン

2-クロロ-5-トリフルオロメチルピリ
ジン 4g に代えて2,3-ジクロロ-5-トリ
フルオロメチルピリジン 4.75g を用いる以
外は前記合成例 2 と同様にして反応を行ない、
後処理を行なって融点 125~128℃ の目
的物 1.9g を得た。

特許出願人 石原産業株式会社

- 8 完 -

EXAMINER'S ROOM.

UNITED STATES PATENT OFFICE.

HERMANN THOMS, OF BERLIN, GERMANY.

PROCESS OF MAKING PARA-PHENETOL CARBAMIDE.

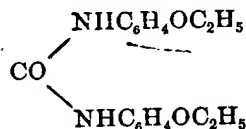
SPECIFICATION forming part of Letters Patent No. 502,504, dated August 1, 1893.

Application filed November 18, 1892. Serial No. 452,446. (Specimens.)

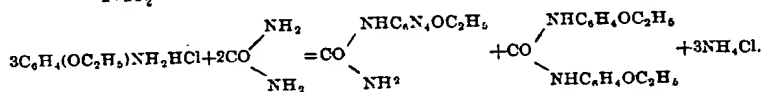
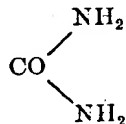
To all whom it may concern:

Be it known that I, HERMANN THOMS, chemist, a subject of the Emperor of Germany, residing in the city of Berlin, German Empire, have invented certain new and useful Improvements in the Production of Para Phenetol Carbamide; and I do hereby declare that the following is a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

My previous researches (published in the *Pharm. Centralhalle*, March 24, 1892,) have shown that di-para-phenetylurea



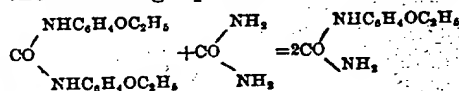
may be readily obtained, in addition to the hydrochlorid of phenetidin, by causing carbonylchlorid to act on a solution of para phenetidin in toluene. Since then I have found that this body, when heated for several hours with common urea



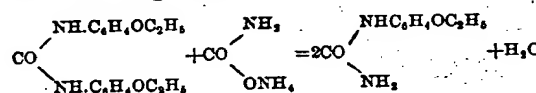
This process will yield, in addition to the para-phenetol carbamide, diparaphenetylurea. The paraphenetolcarbamide crystallizes from the hot filtrate.

The paraphenetolcarbamide obtained as described from diparaphenetylurea, or from paraphenetidin by the action of common urea or the carbamide salt of ammonia, or commercial ammonium carbonate, melts at a temperature approaching 170° centigrade, and has a sweet taste of extraordinary intensity which renders it suitable for industrial application as a sweetening substance. According to physiological experiments, the new substance is quite harmless to the human organism.

in equimolecular proportions in a closed vessel, and at a temperature ranging between 150° and 160° centigrade, is easily converted into the para phenetol carbamide as indicated by the following equation:—



Instead of the common urea the carbamide salt of ammonia or commercial ammonium carbonate may be employed. The reaction takes place in the first case as indicated by the following equation:



I have found also, that instead of the di-paraphenetylurea, paraphenetidin or the hydrochlorid of para-phenetidin may be employed, the latter being either treated in a closed vessel with common urea, or the carbamide salt of ammonia, or with commercial ammonium carbonate at a temperature of 160° centigrade; or an aqueous solution of the hydrochlorid of the paraphenetidin (three molecules) and common urea (two molecules) being heated and kept at the boiling point for a considerable time, the reaction being indicated by the following equation:

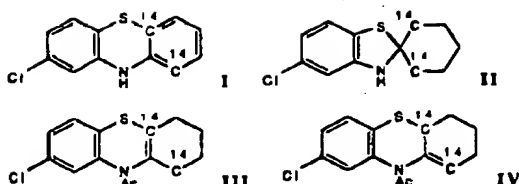
Having thus described my invention, what I claim as new therein, and desire to secure by Letters Patent, is—

1. The process of obtaining paraphenetol carbamide, by the reaction of a para salt of phenetidin on a substance such as common urea in about the proportions set forth.
2. The process of obtaining para-phenetol carbamide, which consists in boiling an aqueous solution of para-phenetidin-hydrochlorid with common urea in about the proportions set forth.

HERMANN THOMS.

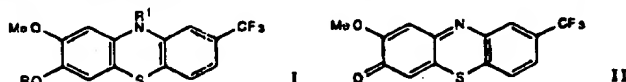
Witnesses:

FRITZ RINDEL,
AUG. FRAHNE.



to give the tetrahydrophenothiazine olefin mixt. III and IV which was directly converted to labeled I via treatment with DDQ in refluxing benzene followed by hydrolysis of the acetyl group.

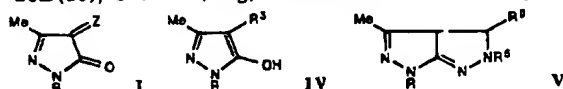
91:74554j Synthesis of 7,8-disubstituted metabolites of trifluorpromazine: 2-(trifluoromethyl)-7,8-dimethoxy-10-[3-(dimethylamino)propyl]-phenothiazine and related compounds. Mittal, R. L.; Mittal, Madhu; Laxmi, V.; Mittal, Suresh; Shukla, A. P. (Dep. Chem., Univ. Rajasthan, Jaipur, 302 004 India). *J. Inst. Chem. (India)* 1978, 50(4), 159-61 (Eng). Phenothiazine I [R = Me, R¹ = (CH₂)₃NMe₂], a



metabolite of trifluorpromazine was prepd. Thus, condensation of 2,4-H₂N(F₃C)C₆H₃SH Zn salt with 2-chloro-5-methoxy-*p*-benzoquinone in refluxing EtOH 4 h gave II quant., II was reduced with Na₂S₂O₄ in aq. Me₂CO to give 90% phenothiazinol I (R = R¹ = H). The product was O-methylated with Me₂SO₄ in Me₂CO contg. Na₂S₂O₄ and aq. KOH 4 h at 60° and the product other I (R = Me, R¹ = H) (67% yield) was N-alkylated by Cl(CH₂)₃NMe₂ in Me₂SO contg. NaH 2 h at room temp. to give I [R = Me, R¹ = (CH₂)₃NMe₂], characterized as its maleate.

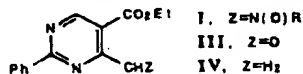
DIAZINES

91:74555k Reactions of 3-methyl-1-aryl-Δ²-pyrazolin-5-ones with aromatic aldehydes, aryl diazonium chlorides and of their products 3-methyl-1-aryl-4-arylidene-Δ²-pyrazolin-5-ones with secondary amines, hydrazines, dialkyl phosphites, Grignard reagents, ethyl aceto- or cyanoacetate and cyclohexanone. Zimaity, T.; Afsah, E.; Abbas, M. (Fac. Sci., Mansoura Univ., Mansoura, Egypt). *Indian J. Chem., Sect. B* 1978, 16B(10), 876-9 (Eng). Reactions of I (R = *p*-ClC₆H₄),



p-O₂NC₆H₄; Z = H₂ (II) with R¹CHO (R¹ = *p*-MeOC₆H₄, O₂NC₆H₄, Me₂NC₆H₄; thienyl) gave I (Z = CHR¹) (III). II and *p*-ClC₆H₄N₂Cl gave I (Z = H, N:NC₆H₄-Cl-*p*). Mannich reaction of II gave I (Z = H, R²NHCH₂; R² = *p*-ClC₆H₄, Me). III and piperidine gave IV (R³ = *p*-MeOC₆H₄CH₂R⁴, R⁴ = piperidino, etc.). Cyclization of III with N₂H₄ and PhNHNH₂ gave V (R⁵ = Ph, H; R⁶ = *p*-MeOC₆H₄ etc.). Reactions of II with dialkyl phosphite, Grignard reagents, Et acetoacetate, NCCH₂CO₂Et and cyclohexanone gave compds. related to I and IV.

91:74556m Synthesis and biological activity of α-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinyl)-N-substituted nitrones. Roy, S. K.; Rao, K. Srinivasa; Reddi, G. S.; Sachdeva, Meena (Res. Dev. Dep., Indian Drugs and Pharm. Ltd., Hyderabad, India). *Indian J. Chem., Sect. B* 1978, 16B(10), 907-9 (Eng).

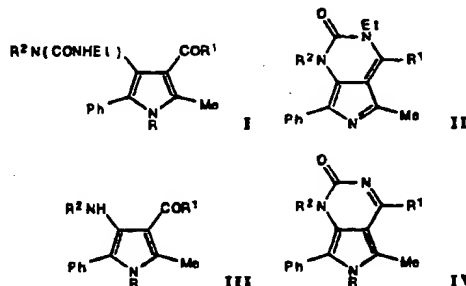


Title compds. I (R = Et, Pr, Bu, CH₂CH₂OH, Ph, PhCH₂, *o*-MeC₆H₄, *p*-ClC₆H₄ (II), *p*-MeSO₂C₆H₄) were prepd. by treating RNHOH with pyrimidinecarboxaldehyde III, which was prepd. by Kroehnke oxidn. of IV. I at 25-200 μg/mL were fungicidal against dematophytes. II killed *Mycobacterium tuberculosis* at 25 μg/mL.

91:74557n Pyrimidines. Part LXXVI. *tert*-Butylation of quinazoline. De Bie, D. A.; Nagel, A.; Van der Plas, H. C.; Geurtsen, G.; Koudijs, A. (Lab. Org. Chem., Agric. Univ., Wageningen, Neth.). *Tetrahedron Lett.* 1979, (7), 649-52 (Eng). Quinazoline (I) is present in soln. at pH 3 as its cationic covalent hydrate; and treatment of an aq. soln. of I with excess Me₃CCO₂H and ammonium peroxydisulfate, in the presence of a catalytic amt. of AgNO₃ at 40° and at pH 1, gave 2-*tert*-butyl-3,4-dihydro-4-oxoquinazoline (II), quant. Similar treatment of I at 70° and at pH 5 for 2 h gave a 4:3:2 mixt. of 2-*tert*-butylquinazoline (III), 4-*tert*-butylquinazoline (IV), and 2,4-di-*tert*-butylquinazoline (V), whereas similar treatment of I at 70° and at pH 4 gave mainly 2-HCOC₆H₄NHCHO and 2-HCOC₆H₄NH₂ (VI). At pH 3, VI was the main product together with III, IV,

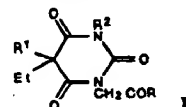
V, and 4-*tert*-butyl-3,4-dihydroquinazoline. The formation of II, III, IV, V, and VI is discussed.

91:74558p Synthesis and antiinflammatory properties of some pyrrole(1H,3H)[3,4-d]pyrimidin-2-ones and pyrrole(1H,6H)[3,4-d]pyrimidin-2-on s. Tarzia, G.; Panzone, G.; Schiatti, P.; Selva, D. (Dep. Org. Chem., Lepetit Res. Lab., Milan, Italy). *Farmaco, Ed. Sci.* 1979, 34(4), 316-30 (Eng).



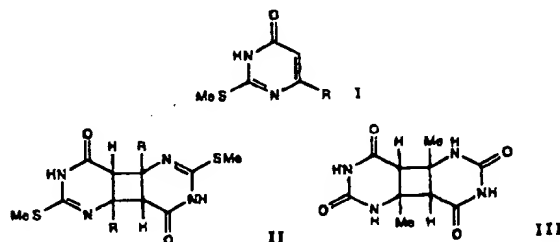
The cyclocondensation reaction of pyrroles I (R = H, Me, Et; R¹ = Me, Ph; R² = Et, H, CHMe₂) in MeOH contg. HCl yielded pyrrolopyrimidinones II, and III (R, R¹, and R² same as above), which reacted with NaOCN at room temp. to give IV; II and IV exhibited antiinflammatory activity. III (R = R² = Et, R¹ = Me) in HOAc was added to NaOCN in H₂O, and the mixt. was kept 4 h at room temp. to give IV (R = R² = Et, R¹ = Me).

91:74559q Synthesis and pharmacological screening of some N-carboxymethylbarbituric acid derivatives. I. Mirek, Julian; Adamczyk, Maciej; Chojnacka-Wojcik, Ewa; Naparzewska, Anna (Inst. Chem., Jagellonian Univ., 30-060 Krakow, Pol.). *Pol. J. Pharmacol. Pharm.* 1978, 30(5), 685-93 (Eng). Methylphenobarbital or barbituric acid were N-alkylated with



ClCH₂CO₂Me or BrCH₂CO₂Et in PhMe contg. K₂CO₃ to give 87-90% carbalkoxy derivs. I (R = OMe, OEt, R¹ = Ph, R² = Me) or 85-6% I (R = OMe, R² = CH₂CO₂Me, R = OEt, R¹ = CH₂CO₂Et, R¹ = Et). Hydrolysis of these esters with refluxing concd. HCl gave 90% I (R = OH, R¹ = Ph, R² = Me) or 95% I (R = OH, R¹ = Et, R² = CH₂CO₂H) which were converted into 95% the corresponding acid chlorides with SOCl₂. I (R = Cl, R¹ = Ph, R² = Me) was treated with 2 mol-equiv amines to give 82-90% amides I (R = 2-, 4-HO₂CC₆H₄NH, 3-pyridylamino, 4-pyridylmethylamino). I (R = Cl, R¹ = Et, R² = CH₂COCl) was treated with 4 mol-equiv amines to give 89-92% diamides I (R = 2-, 4-HO₂CC₆H₄NH, 3-pyridylamino, 4-pyridylmethylamino, morpholino; R¹ = RCOCH₂). The amides had no anticonvulsant activity and showed only slight sedative and analgesic action.

91:74560h Photolysis of thiopyrimidine derivatives. Part II. 2-(Methylthio)-6-methyluracil and 2-(methylthio)-6-ethyluracil. Golankiewicz, Krzysztof; Szajda, Maria; Wyrzykiewicz, Elzbieta (Inst. Chem., A. Mickiewicz Univ., 60780 Poznan, Pol.). *Pol. J. Chem.* 1979, 53(2), 529-31 (Eng). Irradn. of I (R = Me.



Et) in Me₂CO at λ > 254 nm gives 20.5% II (R = Me, Et); irradiation of aq. II at 254 nm gave I. The hydrolysis of II (R = Me) gave III which on irradiation (in acidic, basic, or neutral H₂O) at 254 nm gave 6-methyluracil; this established the anti-configuration for II (R = Me). The photodimerization of I (R = CO₂H) was contrasted to the lack of photodimerization of I (R = CO₂H).

91:74561j Succinate dehydrogenase inhibitory activity of new 1-aryl-3-(N,N-dimethylaminopropyl)thiobarbiturates. Tripathi, Shephali; Pandey, B. R.; Raman, K.; Barthwal, J. P.; Kishor, K.; Bhargava, K. P. (King George's Med. Coll., Lucknow Univ., Lucknow, India). *Eur. J. Med. Chem. - Chim. Ther.* 1979, 14(2), 133-4 (Eng). Thiobarbiturates I (R = Ph, isomeric tolyl, xylyl, or anisyl, 2-EtOC₆H₄, 2- or 4-ClC₆H₄, 4-BrC₆H₄) were prepd. by treating Me₂NCH₂CH₂CH₂NH₂ with RNCS and cyclocondensing product thiourea Me₂NCH₂CH₂CH₂NHCSNHR with malonic acid. I inhibited (15.1-75.50%) succinate dehydrogenase in vitro activity of rat brain homogenate.